Original article

Factors associated with improvement in the severity of major depressive disorder 5 to 11 weeks after initiating treatment with antidepressants

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Objectives To identify factors associated with symptom improvement in patients with major depressive disorder (MDD) at 5 to 11 weeks after initiating treatment with antidepressants.

Methods This observational clinical research study was based on data from a retrospective chart review. The patient population included individuals treated at the outpatient unit of the Department of Psychiatry of Siriraj Hospital (Bangkok, Thailand) who had been diagnosed for the first time with MDD according to criteria in the Diagnostic & Statistical Manual of Mental Disorders, 5th edition either by a psychiatrist or by a psychiatric resident under the supervision of a psychiatrist. Patient symptom severity was evaluated at the first visit using the Thai version of the Montgomery and Asberg Depression Rating Scale (MADRS) and was reevaluated 5 to 11 weeks after initiation of treatment.

Results The mean age of the 114 patients was 37.56±16.131 years and the majority (n=84 or 73.7%) were female. Treatment with an adequate dose of an anti-depressant for an sufficient period of time (> 5 weeks) (OR, 15.344; 95% CI, 1.756-134.119; $p = 0.014$) was associated with early remission of symptoms. Anti-depressant use at an adequate dose and for a sufficient period of time (OR 9.224; 95% CI 1.786-47.632; $p = 0.008$) was associated with symptom response.

Conclusion Use of an appropriate anti-depressant for at least 5 weeks is associated with early remission of depressive symptoms. Titrating antidepressants to an adequate dose and encouraging patients to continue their use for an adequate period can help improve treatment outcomes including MADRS scores. **Chiang Mai Medical Journal 2020;59(2): 45-51.**

Keywords: early remission, symptom improvement, major depressive disorder, MDD

Introduction

Depressive disorder is currently one of a psychiatric disorder affecting a high number of patients, causing significant dysfunction in activities of daily living and work life. The World Health Organization estimates the number of patients affected by depressive disorders be > 300 million globally (1). It has been estimated that up to one-eighth of the population of the United States lives with major depressive disorder (MDD). Depression is the second-highest ranked disease leading to loss of the ability to work (2). Kongsuk et al. reported

that in Thailand 626,332 individuals diagnosed with depressive disorder(s) received medication and/or psychological therapy in 2015. By 2016, the number of patients undergoing treatment for depressive disorder had increased by over 10% to 694,334 (3).

Symptom improvement is the treatment goal in patients with depressive disorders because the disorder affects their daily life and long-term prognosis (4). The definition of symptom remission in MDD is a total Montgomery and Asberg

Depression Rating Scale (MADRS) score ≤ 10 (5), and the definition of treatment response is a decrease in total MADRS score > 50% after the first initiation of treatment (6). Symptom improvement in individuals with depressive disorders is related to many factors. Riedel et al. demonstrated reported that remission could be predicted by a lower Hamilton Depression Rating Scale-21 Item (HAMD-21) baseline score, episode duration < 24 months, and fewer previous hospitalizations (7). Additionally, Katzelnick et al. reported three factors that could predict the probability of remission in patients with depression: severity of initial Patient Health Questionnaire-9 (PHQ-9) score; number of weeks to first follow-up; and documented self-management efforts (8). Sakurai et al. demonstrated that early improvement in sad moods, feelings of sluggishness, low energy, restlessness, and negative self-view were significantly associated with subsequent remission in the treatment of MDD (9). Swindle et al. reported three categories of risk factors for sustained nonremission: demographic older, male, low education level, lack of initial employment); diagnostic history (presence of secondary major depression; family history of affective disorder; longer duration of the episode before admission; previous treatment; lack of relationships; and greater initial symptom severity); and life context (ongoing stressful circumstances, low number and quality of close relationships, and poor coping skills) (10).

Early remission and early improvement of symptoms tend to be associated with a better prognosis in individuals with MDD. Therefore, identifying relevant related factors is important because it could be helpful in treatment planning. However, studies addressing major depressive disorder in Thailand have mainly focused on prevalence, incidence, depression-related factors, and rating scale scores(11), with few studies investigating symptom remission or treatment response.

Objectives

The present study aimed to identify factors associated with symptom remission and treatment response in patients with MDD 5 to 11 weeks after initial treatment.

Methods

Study design and subjects

This cross-sectional study was approved by the Siriraj Research Affair and the Siriraj Institutional Review Board (SIRB), Faculty of Medicine, Siriraj Hospital, Mahidol University (Bangkok, Thailand; CoA No.676/2560 EC3).

Charts of patients who were newly diagnosed with MDD according to the Diagnostic & Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria(12) at the Outpatient Unit of the Department of Psychiatry, Siriraj Hospital, between January 2015 and September 2017, were reviewed. Only patients diagnosed by psychiatrists or psychiatric residents in training under the supervision of psychiatrists were included in this study.

The charts reviewed in this study were those of patients > 18 years of age documented their first visit to the psychiatric outpatient unit and included an evaluation of the severity of their depression using the Thai version of the MADRS at the first visit and after 5 to 11 weeks (< 3 months) of receiving treatment.

Patients whose initial diagnosis was changed to another diagnosis, e.g., to bipolar disorder or schizoaffective disorder, a subsequent after the initial visit were excluded.

Instruments

The Thai version of the MADRS consists of 10 questions, each scored from 0 to 6. A cut-off total score of ≤ 10 at the final follow-up visit was defined as remission. Response was defined as a 50% decrease from the initial score. The scores at the final follow-up also had to be above the remission threshold to be considered a response (5). The Thai version of the MADRS has demonstrated sensitivity, specificity, and positive and negative predictive values equivalent to 100 and the overall Cronbach's alpha internal consistency has been reported to be 0.9637 (13).

The case record form was comprised of two parts as follows:

1. Demographic characteristics, including sex, age, education level, occupation, marital status,

support system, psychotic symptom(s), duration of symptom(s), stressors, comorbidities in psychiatric disorders, history of substance use, comorbidities in physical diseases, a history of familial psychiatric disorders, type and duration of use of medication for treatment of MDD and psychotherapy.

2. MADRS scores were evaluated at the first visit and at 5 to 11 weeks after initiation of treatment (total scores and item scores).

The collected data were analyzed using SPSS (IBM Corporation, Chicago, IL, USA). Statistical tests included Pearson's chi-squared test, Fisher's exact test, and logistic regression.

Data collection

Data were gathered after receipt of approval from the Ethics Committee for Human Research. Data were collected from SiIT, the Siriraj Hospital's patient charting system. Data were recorded in case record forms designed by the research team and based on information from previous studies.

Case record forms do not list patient name, hospital number, or other details that could be used to identify patients. A numerical code was used instead.

Independent variables included age, duration of symptom(s), and severity of symptom(s) before treatment. Categorical variables included education level, occupation, marital status, support system, and receipt of an adequate dose of medication for a sufficient period of time which was defined as receiving a therapeutic dose of antidepressant for > 5 weeks.

Results

1. Demographic data

Between January 2015 and September 2017, 114 new patients who were diagnosed with MDD and received treatment at the Outpatient Clinic of the Department of Psychiatry, Siriraj Hospital met the inclusion criteria. The average age of the patients was 37.56 years, most were female (73.7%), and more than half were single (58.8%). Most patients graduated with a Bachelor's degree (39.5%), many were currently university students

(24.6%), and most lived with family (71.1%). The antidepressants used by most patients were selective serotonin reuptake inhibitors (SSRIs) (90.4%) (Table 1).

2. Factors associated with remission of MDD 5 to 11 weeks after initial treatment

Factors statistically significantly associated with remission of MDD included male sex (2.69 times the rate for females) and receiving an adequate dose of medication for a sufficient period of time. There were no other statistically significant factors (Table 2). However, when age, gender, occupation, marital status, support system and receipt of an adequate dose of medication for a sufficient period were adjusted for, male sex was no longer statistically significant, but receiving an adequate dose of medication for a sufficient period was still significant compared with an inadequate dose (15.344 times) (Table 4).

3. Factors associated with treatment response of patients with MDD 5 to 11 weeks after initiation of treatment

Receipt of an adequate dose of medication for a sufficient period of time, as well as other factors, was statistically significantly associated with treatment response for both crude and adjusted

Table 1. Demographic data of patients newly diagnosed with major depressive disorder

Demographic factors	n (%)
Female sex	84 (73.7)
Education, Bachelors and above	51 (44.7)
Occupation, employed	98 (86.0)
Marital status, have spouse	32 (28.1)
Support system, live with others	87 (76.3)
Severity of symptom before treatment (total mean ± SD MADRS score before treatment = 28.26±5.846	
Antidepressants usage	
- Selective serotonin reuptake inhibitors	103 (90.4)
- Alpha-2 adrenoceptor antagonists	9 (7.9)
- Others	2 (1.7)

MADRS, Montgomery and Asberg Depression Rating Scale

Table 2. Factors associated with symptom remission of major depressive disorder at 5 to 11 weeks after initiation of treatment

Factor	Crude odds ratio[a] (95% CI)
Age, years (< 30)	1.238 (0.591–2.592)
Male sex	2.884 (1.155–7.203)[c]
Education, Bachelors and above	1.000 (0.419–2.385)
Occupation, employed	1.052 (0.330–3.358)
Marital status, have spouse	0.887 (0.39 –2.014)
Support system, live with others	0.597 (0.215–1.659)
Severity of symptom before treatment, mild to moderate	1.767 (0.571–5.472)
Concentration difficulties, mild disturbance	1.643 (0.768–3.515)
Presence of psychotic symptom, absent	1.240 (0.076–20.325)[b]
Duration of symptom before treatment, < 3 months	1.202 (0.573–2.520)
Presence of stress, absent	1.640 (0.679–3.959)
Comorbidity in psychiatric disorder, absent	0.917 (0.296–2.836)
Substance use, absent	0.381 (0.038–3.782)[b]
Comorbidity in physical disease, absent	1.185 (0.564–2.490)
Presence of familial psychiatric disorder, absent	1.270 (0.526–3.066)
Receive adequate dose of medication for adequate duration	5.500 (1.443–20.959)[c]
Received psychotherapy, yes	2.313 (1.869–2.862)[b]

[a] Pearson's chi-squared test, [b] Fisher's exact test, [c] $P < 0.05$

Table 3. Factors associated with treatment response in patients with major depressive disorder at 5 to 11 weeks after treatment

Factor	Odds ratio[a] (95% CI)
Age, years (< 30)	1.247 (0.588–2.646)
Male sex	1.429 (0.596–3.425)
Education, Bachelors and above	0.696 (0.288–1.685)
Occupation, employed	1.353 (0.423–4.333)
Marital status, has spouse	0.654 (0.286–1.495)
Support system, lives with others	0.788 (0.283–2.196)
Severity of symptom before treatment, mild to moderate	0.833 (0.260–2.669)
Concentration difficulties, mild disturbance	1.286 (0.596–2.774)
Presence of psychotic symptoms, absent	1.545[b] (0.094–25.354)
Duration of symptoms before treatment, < 3 months	1.173 (0.552–2.489)
Presence of stress, absent	1.010 (0.422–2.419)
Comorbid psychiatric disorder, absent	0.833 (0.260–2.669)
Substance use, absent	0.481[b] (0.048–4.776)
Comorbid physical disease, absent	1.138 (0.535–2.419)
Presence of familial psychiatric disorder, absent	1.393 (0.573–3.385)
Receive adequate dose of medication for a sufficient period of time	4.643[c] (1.357–15.887)
Receive psychotherapy - yes	0.316[b] (0.028 – 3.594)

[a] Pearson's chi-squared test, [b] Fisher's exact test, [c] $P < 0.05$

odds ratios (compared with inadequate dose, 9.224 times). No other factors demonstrated statistically significant associations (Tables 3-4).

Discussion

This retrospective study investigated factors associated with symptom remission and treatment

Table 4. Adjusted odds ratios show the association between factors with treatment symptom response and remission of major depressive disorder at 5 to 11 weeks after initiation of treatment

Factors	Adjusted odds ratio[a] (95% CI)	
	Treatment response	**Remission**
Age < 30 years	0.828 (0.315-2.176)	1.023 (0.385-2.717)
Male sex	1.154 (0.440-3.026)	2.737 (0.991-7.557)
Occupation, employed	1.172 (0.317-4.332)	0.765 (0.192-3.042)
Marital status, have spouse	0.695 (0.245-1.967)	1.274 (0.436-3.723)
Support system, live with others	0.565 (0.168-1.902)	0.291 (0.080-1.057)
Receipt of an adequate dose of medication for a sufficient period	9.224 (1.786-47.632)[b]	15.344 (1.756-134.119)[b]

[a]Multiple logistic regression, [b]$p < 0.05$

response of patients with MDD 5 to 11 weeks of after initiation of treatment.

One factor associated with both symptom remission and treatment response was receiving an adequate dose of medication for a sufficient period of time, which increased the chances of remission by a factor of 15.344 and increased the chance of treatment response by a factor of 9.224. This can be explained by the mechanism of the medication. When antidepressants, such as a selective serotonin reuptake inhibitor, are administered, it does not immediately lead to elevated levels of serotonin (5HT). Rather, 5HT will increase in the somato-dendritic area of serotonergic neurons first, which causes 5HT1A auto-receptors to become desensitized. Because the neuron no longer inhibits its own secretions, there is an increased release of serotonin at the axon terminal. However, the course of this process over time is correlated with the onset of the therapeutic actions of the medication (14).

Our results are consistent with those reported by Melfi et al., who found that factors affecting relapse and recurrence included comorbidities, race, and medical guideline adherence. However, discontinuing antidepressants too early was very likely to result in relapse or recurrence (15). Other factors, including age, education level, occupation, marital status, support system, total MADRS score evaluated at the first visit, difficulties with concentration, presence or absence of psychotic symptoms, duration of symptoms before treatment, presence of stress after treatment, comorbid

psychiatric disorder(s), a history of substance use, comorbid physical disorder(s), the presence or absence of familial psychiatric disorders, and receiving psychotherapy, had no statistically significant relationship with improvement in disease severity 5 to 11 weeks after initiation of treatment. This is inconsistent with previous studies (7–10), but may be explained by the small sample size in the current study. Previous studies have shown that physical condition and comorbidities can affect the severity and course of depressive symptoms; however, our study demonstrated that taking adequate medication can overcome those obstacles.

The range of follow up duration is one of the limitations in this study as it depended on the severity of the patients' symptoms and the clinical judgement of physicians. The duration of the period to follow up varied from 5 weeks to 11 weeks, but did not exceed 12 weeks.

The present study was conducted at a university hospital, which uses a scale system to measure symptom severity as a factor in determining adjustments to antidepressants. All cases are evaluated both by residents in training and by consultant psychiatrists. Additionally, in this study, 44.7% of patients had comorbid physical conditions; hence, the results may not be generalizable to other hospital settings. This study can, however, be used as a reference for further research investigating treatment outcomes of patients with MDD treated at a tertiary hospital.

Conclusions

Use of an appropriate anti-depressant for at least 5 weeks is associated with early remission of depressive symptoms. Titrating antidepressants to an adequate dose and encouraging patients to continue their use for at least 5 weeks can help improve treatment outcomes as indicated both by patient reports of symptoms as well as by MADRS scores.

Author contributions

JL, PP and KW contributed to the conceptual design of the study. JL contributed to the collection and interpretation of the data. JL, PP and KW contributed to writing the manuscript and submission of the study. All authors reviewed and agreed with the content of the manuscript.

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Competing interests

None declared.

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ปัจจัยที่สัมพันธ์กับระดับอาการที่ดีขึ้นของโรคซึมเศร้าภายหลังการรักษา 5 ถึง 11 สัปดาห์ ด้วยยาต้านเศร้า

จุฑาวดี หล่อตระกูล, ปเนต ผู้กฤตยาคามี, ณัฏฐา สายเสวย, สุนันทา ฉันทกาญจน์ และ กมลพร วรรณฤทธิ์

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วัตถุประสงค์ เพื่อศึกษาปัจจัยที่มีความสัมพันธ์กับระดับอาการที่ดีขึ้นของโรคซึมเศร้า (major depressive disorder) ภายหลังการรักษา 5-11 สัปดาห์

วิธีการ งานวิจัยนี้เป็นการศึกษาแบบวิเคราะห์ข้อมูลย้อนหลัง โดยเก็บข้อมูลจากบันทึกเวชระเบียนผู้ป่วยนอก ซึ่งเป็นผู้ป่วยใหม่ที่ได้รับการวินิจฉัยเป็นโรคซึมเศร้า โดยอ้างอิงตามเกณฑ์ DSM-5 ที่หน่วยตรวจโรคจิตเวช-ศาสตร์ โรงพยาบาลศิริราช โดยอาจารย์จิตแพทย์หรือแพทย์ประจำบ้านสาขาวิชาจิตเวชศาสตร์ และมีการ ประเมินอาการโดยใช้ Montgomery and Asberg Depression Rating Scale (MADRS) ฉบับภาษาไทยใน ครั้งแรกที่รับการรักษาและช่วง 5-11 สัปดาห์ หลังรับการรักษา

ผลการศึกษา จากข้อมูลเวชระเบียนผู้ป่วยจำนวน 114 คน เป็นผู้หญิง 84 คน คิดเป็นร้อยละ 73.7 ของกลุ่ม ตัวอย่าง โดยมีอายุเฉลี่ยอยู่ที่ 37.56 ปี (SD = 16.131) จากการวิเคราะห์ข้อมูลงานวิจัยพบว่าการได้รับยาต้าน เศร้าในระดับที่เหมาะสมครบระยะเวลาที่เหมาะสม (มากกว่า 5 สัปดาห์ขึ้นไป) (OR, 15.344; 95% CI, 1.756-134.119; *p* = 0.014) จะมีความสัมพันธ์อย่างมีนัยสำคัญกับการสงบของอาการ นอกจากนี้ การได้รับยาต้าน เศร้าในระดับที่เหมาะสมครบระยะเวลาที่เหมาะสม (OR 9.224; 95% CI 1.786-47.632; *p* = 0.008) ยังมี ความสัมพันธ์อย่างมีนัยยะสำคัญกับการตอบสนองต่อการรักษาอีกด้วย

สรุป ปัจจัยที่สัมพันธ์กับการทุเลาของอาการของโรคซึมเศร้าในระยะแรก คือ การได้รับยาต้านเศร้าในระดับที่ เหมาะสมอย่างน้อย 5 สัปดาห์ ดังนั้น ผู้รักษาจึงควรให้ความสำคัญในการปรับยาต้านเศร้าให้ได้ขนาดรักษาใน ระยะเวลาที่เหมาะสม เพื่อช่วยผู้ป่วยให้ได้การประเมินคะแนน MADRS ที่ดีขึ้น **เชียงใหม่เวชสาร 2563;59(2): 45-51.**

คำสำคัญ: ระดับอาการที่ดีขึ้น โรคซึมเศร้า การทุเลาของโรคซึมเศร้า